Appendix E1

Tumor Segmentation

To optimize the accuracy of the tumor segmentation, a systematic approach was used to determine the imaging sequence to be used for segmentation. The following describes the approach, and then information about the segmentation software itself is provided. Semiautomatic 3D segmentation of the tumor was performed by using a multiphasic contrast-enhanced MR sequence performed just before surgical therapy. Although ADC maps were generated in the same imaging session, contrast-enhanced MR imaging was selected for segmentation because it offers a higher spatial resolution, which is favorable for a more accurate tumor segmentation (eg, 3.6-fold better resolution for contrast-enhanced MR imaging vs ADC maps on the basis of a voxel size of 1.56× 1.56 × 2.5 mm for contrast-enhanced MR imaging and 1.48 × 1.48 × 10 for ADC maps). Furthermore, contrast-enhanced MR imaging shows higher image contrast as compared with ADC maps, making the delineation of tumor versus healthy tissue more practicable. These characteristics of contrast-enhanced MR imaging allow for a more accurate inclusion of targeted tumor tissue into the 3D segmentation mask for qEASL and qADC calculation. For the qADC calculation in this study, the 3D masks created on contrast-enhanced MR images were transposed onto the ADC maps by using a manual rigid transformation. This image registration step was necessary because of matrix differences between T1- and diffusion-weighted sequences to achieve optimal intermethod comparison as well as to match the T1-based tumor segmentation mask with the diffusion-weighted sequences. The use of the same segmentation mask provides a direct comparison between the two imaging methods and with pathologic examination. Although manual adjustment of the segmentation mask to include additional tumor tissue on ADC maps is possible with this software, no such case was present in the study population on the basis of visual assessment by a radiologist. The segmentation was performed on multiphasic contrast-enhanced MR images obtained in arterial (20 seconds) and portal venous (70 seconds) phases. For the final analysis, the arterial phase was chosen over the portal venous phase because all lesions in the analysis demonstrated much better enhancement in the early phase. Of note, no arterioportal shunting was observed in the selected cases. The tumor segmentation was performed by using in-house software (Medisys; Philips Research, Suresnes, France). This software uses non-Euclidean geometry and theory of radial basis functions, which allows the segmentation of 3D objects with straight edges and corners (25). The algorithm creates image-based masks located in a 3D region whose center and size is defined by the user, yielding the nomenclature “semiautomatic.” After identifying an initial control point, the user can interactively expand or contract the 3D mask. Adjustments of the overall 3D volume of the mask can be interactively performed by placing additional control points. The shape and spatial localization of the final 3D segmented mask (Fig 2, *B* and *C*) is registered to the coordinates within the MR imaging data set and–upon image registration–may be applied to other MR images in the same patient. With the 3D nature of the segmentation, the tumor volume can be directly calculated.

qEASL Technique

To calculate the qEASL values, the following steps were performed:

1. The precontrast MR image was subtracted from the arterial phase image to remove background enhancement (26). This step is of particular importance to achieve an accurate assessment of lesions with hemorrhagic necrosis and helps mitigate false-positive enhancement from contrast enhancement.

2. The 3D segmentation mask from the arterial phase contrast-enhanced MR imaging was transposed onto the subtracted image set from above.

3. A 3D region of interest (ROI) (1 cm^3) was placed into extratumoral liver parenchyma of the subtracted image set to calculate the relative enhancement values within the tumor volume as a reference for normalization (Fig 3, *A*) (23). Additional information about the selection of ROIs is provided below.

4. A threshold based on image enhancement defined viable tumor tissue as voxels within the 3D mask where the enhancement exceeded the average +2 standard deviation value of the ROI. Additional information about the calculation of the ROI-based threshold is provided below.

5. To estimate tumor necrosis according to qEASL, nonenhancing regions of the tumor (voxels with enhancement less than the ROI threshold) were assumed to be largely necrotic (1) and expressed as a percentage of the previously calculated overall tumor volume.

6. A normalized color map overlay on the arterial phase MR image was used to demonstrate regional tumor enhancement heterogeneity (Fig 3, *A,* with red representing maximum enhancement and/or viable tumor and blue representing no enhancement, below the threshold and/or necrotic tumor tissue) (18). Additional information on color coding is provided below.

qADC Technique

The qADC calculation used a similar methodology as described for qEASL. However, image subtraction was omitted (not necessary owing to the nature of ADC map calculation) and so measurements were directly performed on the ADC maps. Several previous studies demonstrated a high degree of correlation between ADC values and tumor necrosis after TACE, showing greater ADC values in necrotic tumor tissue (37,38). Furthermore, by nature of the calculation, signal intensities in ADC maps are directly proportional to the ADC values. Therefore, tumor necrosis appears as regions of high signal intensity, whereas viable tumor tissue shows low signal intensity (39). As mentioned earlier, the previously created 3D segmentation mask on the contrast-enhanced MR image was transposed to the ADC map and manually registered with the corresponding arterial phase image. From here, the following steps were performed to calculate qADC:

1. To calculate the relative ADC signal intensity values within the tumor volume, a 3D ROI (1 cm^3) was placed into extratumoral liver parenchyma (Fig 3, *B*).

2. Necrotic tumor tissue was then defined as areas where the ADC signal intensity exceeded the average value +2 standard deviations of the ROI, which was used as a threshold. Additional information on the selection of ROIs is provided below.

3. To estimate tumor necrosis according to qADC, hyperintense areas within the 3D mask were expressed as a percentage of the previously calculated overall tumor volume.

4. To maintain a uniform color code as that used for qEASL, a reverse color map overlay was used (Fig 3, *B*, with red representing minimum signal intensity and/or viable, least diffusion restricted tumor and blue representing maximum signal intensity and/or necrotic tumor tissue). Additional information on color coding is provided below.

Definition of the ROI and Color Coding

Unlike fully automated segmentation techniques, a semiautomated approach allows the combination of software-based image processing with manual adjustments by a radiologic image reader. The goal of ROI selection in this study was to achieve an intuitive approach, resembling the gold standard of a radiologic reading. Practically, a radiologic image reader compares enhancement and/or diffusion properties of the tumor with that of the nontumoral liver tissue rather than extrahepatic tissue. Several ROI localizations (including extrahepatic ROIs within nonenhancing soft tissue [eg, Psoas muscle]) were considered; however, they appeared to be counterintuitive and failed to provide consistent results. Several studies demonstrated the liver lobe dependency of ADC values as well as contrast enhancement, prompting us to select ROIs within the ipsilateral liver lobe containing the target lesions (40,41). The abnormal enhancement patterns of cirrhotic livers were taken into account when selecting the localization of an ROI. Accordingly, ROIs were placed within visually nonenhancing tissue on the postsubtraction arterial phase image. Furthermore, to avoid corrupted ROIs within focally cirrhotic liver tissue, signal intensity statistics were calculated for every 3D ($1 \times 1 \times 1 = 1$ cm^3) ROI with the goal of achieving a maximum of signal homogeneity. This was performed as follows:

1. A 1 cm^3 ROI was placed in a location as described above (ipsilateral liver lobe, nonenhancing and/or non–diffusion-restricted extratumoral areas).

2. The software provided the minimum and maximum voxel brightness values within the cubic ROI. The numeric output was in patient-specific arbitrary units (AUs) for each ROI. The software furthermore calculated the mean brightness value, standard deviation, and coefficient of variation. Empirically, a coefficient of variation of less than 30% was seen as acceptable, whereas a coefficient of variation greater than 30% was rejected, leading to ROI repositioning.

3. The mean brightness value ± 2 standard deviations was selected as a cutoff (threshold), with all values above seen as real contrast enhancement and/or diffusion restriction. For qEASL, areas lower than the threshold (nonenhancing) were categorized as necrotic. For qEASL, areas with higher signal intensity than the threshold (diffusion restriction) were categorized as necrotic.

4. On the basis of the selected ROI and the mean brightness value, a patient-specific (normalized) 3D color map was overlaid onto the tumor tissue enclosed by the segmentation mask. For qEASL, the color blue was identified as areas with equal and/or lower signal intensity as the mean brightness value ± 2 standard deviations, whereas all signal intensity exceeding this value was coded as an equally distributed histogram of tissue enhancement. The range of enhancement in AU was coded in color shades (aqua, yellow, red), with red representing the maximum signal intensity for a particular patient. The same method was used for qADC color maps; however, color coding was reversed with maximum signal intensity and/or diffusion restriction coded as blue to keep consistent with qEASL.

References

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